

APRIL 2021

# LIVING WITH CANCER



## COLORECTAL CANCER RESEARCH & PRACTICE UPDATES

Colorectal Cancer Canada curates monthly Research & Practice Updates to inform patients and their loved ones of new innovations in colorectal cancer care. The following updates extend from April 1<sup>st</sup> 2021 to April 30<sup>th</sup>, 2021 inclusive and are intended for informational purposes only

### APRIL 2021 PREVIEW

<b>SYSTEMIC THERAPIES, SURGERY &amp; SCREENING .....</b>	<b>2</b>
Understanding early age onset CRC incidence .....	2
FDA Oks marketing of first AI device used to detect lesions during colonoscopy .....	5
Periodontal disease can be a potential risk indicator for colorectal cancer .....	6
Safety and efficacy of 7 days on/7 days off vs 14 days on/7 days off schedules of capecitabine in patients with metastatic colorectal cancer .....	9
Molecular characteristics of early-onset colorectal cancer appear to vary by race.....	10



## SYSTEMIC THERAPIES, SURGERY & SCREENING

### Understanding early age onset CRC incidence

April 2021

*Adapted from an interview with Dr. Kimmie Ng from the ASCO Post*

Despite the decline in the overall incidence of colorectal cancer (CRC) in Canada, there has been an alarming increase in the incidence of CRC in younger adults below the age of 50<sup>1</sup>. Similar trends in the US prompted the American Cancer Society (ACS) in 2018 to lower the CRC screening age from 50 to 45 years for individuals at average risk. The change in screening guidelines was further supported by research from the ACS that demonstrated that people below the age of 55 are 58% more likely to be diagnosed with later-stage disease than older adults, an important factor that negatively impacts patients' outcomes<sup>2</sup>.

Dr. Kimmie Ng is the co-director of the Colon and Rectal Cancer Center and Director of the Young-Onset Colorectal Cancer Center at Dana-Farber Cancer Institute. In her experience, she has found that while the increase in CRC incidence parallels the increasing rates of obesity among the general population in the US, most of the young patients that she sees diagnosed with late-stage disease are physically fit and do not have other common risk factors, such as a family history of the disease, sedentary behaviour, or poor diet patterns. Current research aims to gather deeper information about early-life risk factors such as antibiotic use and early life environments (including psychological and/or physical stresses), as well as recent environmental exposures that are not traditionally associated with CRC. The underlying biological mechanisms that connect these risk factors with early age onset CRC incidence are yet to be understood, such that more targeted therapies may be recommended for patients.

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<sup>1</sup> The incidence of young-onset colorectal cancer in Canada continues to increase  
<https://pubmed.ncbi.nlm.nih.gov/32998071/>

<sup>2</sup> Siegel RL, Fedewa SA, Anderson WF, et al: Colorectal cancer incidence patterns in the United States, 1974-2013. *J Natl Cancer Inst* 109(8):djw322, 2017.

## The molecular makeup of early age onset CRC is different than that of older patients

Findings from a 2019 study found that CRC tumours are not only molecularly distinct from tumours from adults aged 50 and older but also differ between age groups of younger patients. For example, CRC patients between 18-29 years tended to have unique mutations that differed from other age groups of young CRC patients, and young patients with predisposing conditions such as inflammatory bowel diseases or a hereditary syndrome. Among the younger subsets of early age CRC patients, the chance of having any mutation in the MAPK pathway (including BRAFV600E mutations or KRAS mutations) was lower compared to other early age subgroups<sup>3</sup>. Young patients also tend to have more tumours that are microsatellite instability-high (MSI-H) - an important biomarker that predicts better response rates to immunotherapy treatment. Dr. Ng notes that there is no unique molecular “signature” that clearly distinguishes early-onset from late-onset CRC. Determining whether this unique molecular signature exists among early-onset CRC so that a more targeted treatment could be offered remains an important research goal of Dr. Ng and her team.

To address these needs, Dana-Farber/Brigham and Women’s Cancer Center established the [Young-Onset Colorectal Cancer Center](#) to provide early age CRC patients a holistic approach to cancer care. According to Dr. Ng, the director of the new center, cancer care will involve a multidisciplinary team to address the unique needs of young adults including psychosocial and physical concerns, fertility and sexual health, genetic evaluation, young-adult focused support groups, as well as genomic sequencing performed on every patient’s tumour to allow for optimal personalized treatment recommendations.

In Canada, the [Young Adult Colorectal Cancer Clinic](#) located at Sunnybrook Hospital in Toronto offers holistic cancer care to young adults with CRC to address the unique issues due to both the cancer and cancer treatment. A multidisciplinary team of oncologists, social workers, psychologists, geneticists, and a nurse navigator helps to create an individualized treatment plan to provide optimal support to each patient. Family doctors and specialists can refer patients to the Clinic using their [e-referral form](#).

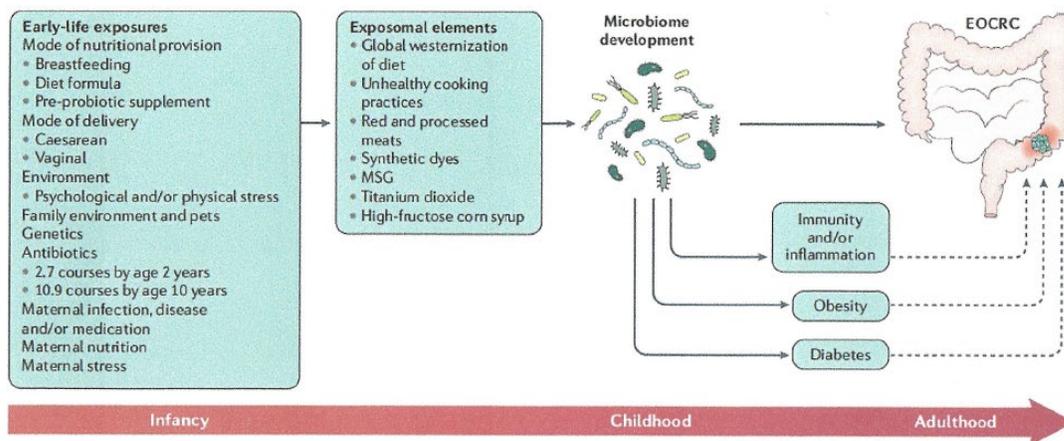
## The role of the gut microbiome in early age onset CRC

An important focus of research on early age CRC is the role of the gut microbiome in the development of the disease. Since the microbiome is influenced by everything from diet to antibiotic use and obesity, and it plays an important role in mediating immune responses in the body, it is believed to be involved in the development of cancer as well as mediating the immune environment of these tumours, affecting how people with cancer respond to treatment.

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<sup>3</sup> Willauer AN, Liu Y, Pereira AAL, et al: Clinical and molecular characterization of early-onset colorectal cancer. *Cancer* 125:2002-2010, 2019.

## Putative early-life and environmental exposures



Hofseth LJ, et al. *Nature Rev Gastroenterol Hepatol* 2020; 17: 352-64.

### Ongoing International Projects

The **Beyond CRC Project** aims to gain a better understanding of young onset CRC by identifying the underlying biological mechanisms of cancer cells, identify risk factors for developing CRC at a young age, and facilitate the development of new therapy options<sup>4</sup>. It aims to assemble a large population of young patients through collaboration with other cancer centers in the US to gather extensive diet and lifestyle data, genetic sequencing information, and tissue, blood, and stool samples from young patients. Patients are asked at an early appointment to be part of a “biobank” of clinical data to form a new longitudinal study of early-onset CRC patients.

The project involves three components: gathering clinical and treatment data; tumour, blood, and stool samples; and a comprehensive diet and lifestyle questionnaire. Stool samples may be gathered via mail-in kits. All these components will be studied alongside information from each patient’s medical record and tumour sample. With hope, the analysis of these components will shed light on the underlying biological mechanisms of the disease.

The Cancer Research UK Grand Challenge **OPTIMISTIC** (Opportunity to Investigate the Microbiome’s Impact on Science and Treatment in Colorectal Cancer) Project to investigate the role of the microbiome in young-onset CRC. The goal of the international collaboration is to discover how the microbiome impacts the development of CRC, and to translate their findings into strategies to improve response to treatment and disease outcomes.

<sup>4</sup> Young Onset Colorectal Cancer Centre Newsletter

[https://www.dana-farber.org/uploadedFiles/Pages/For\\_Patients\\_and\\_Families/Care\\_and\\_Treatment/Treatment\\_Centers/Gastrointestinal\\_Cancer\\_Treatment\\_Center/Cancer\\_Types\\_and\\_Programs/Young-Onset\\_Colorectal\\_Cancer\\_Center/young-onset-newsletter\\_1.pdf](https://www.dana-farber.org/uploadedFiles/Pages/For_Patients_and_Families/Care_and_Treatment/Treatment_Centers/Gastrointestinal_Cancer_Treatment_Center/Cancer_Types_and_Programs/Young-Onset_Colorectal_Cancer_Center/young-onset-newsletter_1.pdf)

[Count me In](#) is a non-profit organization established in 2018 to make it possible for cancer patients anywhere in the US and Canada to share their medical history and experiences and participate in advancing patient-partnered research to speed the development of future therapies. Through a digital social media platform, patients can directly engage with clinicians and researchers. With patient consent, the de-identified clinical data can be accessed freely and rapidly by biomedical researchers everywhere. The platform allows for much more rapid collection of biospecimens (blood, tumour tissue, stool samples), enhancing the diversity and inclusion of diverse racial/ethnic, socioeconomic, and geographical patient data, as well as permitting the continuation of research efforts during the pandemic.

Real-world patient information is often never collected or made available for clinical study. An important reason for this is that many cancer patients receive treatments in community hospitals and clinics, not at large academic medical centres that conduct cancer research. **Count Me In** aims to unite patients and researchers to facilitate a collaborative approach that might unlock critical insights needed to develop new therapies. With a patient-centered approach, patients can help researchers develop better research questions and reach previously hard-to-reach communities of patients. Especially for patients of colour who are underrepresented in cancer research, this project enables their data to be counted in and considered when investigating new treatment approaches.

Currently, four projects have been launched – the Metastatic Breast Cancer Project, the Angiosarcoma Project, the Metastatic Prostate Cancer Project, and the Gastroesophageal Cancer Project. So far, thousands of patients have donated their medical records, tumour samples, and genomic information. Over the next few years, **Count Me In** plans to launch additional projects in all major cancer types including colorectal cancer. The Colorectal Cancer Project is enrolling soon.

**Take away message:**

Rising incidence in early age onset colorectal cancer (CRC) has stimulated many research efforts to be directed towards gaining a better understanding of the mechanisms underlying CRC development in young adults. Research continues to investigate the impact of risk factors such as lifestyle, diet, obesity, and the gut microbiome on early age onset CRC.

[READ THE FULL ARTICLE](#)

**FDA Ok's marketing of first AI device used to detect lesions during colonoscopy**

April 2021

The US Food and Drug Administration (FDA) recently approved the marketing of the **GI Genius**, a system that uses artificial intelligence (AI) technology to aid in the detection of potentially cancerous polyps during a colonoscopy. During a colonoscopy, the technology highlights portions of interest of the colon and generates markers which are superimposed onto the video generated

by the colonoscope camera in real time. These markers help to draw attention to areas of the colon that may require further assessment.



The FDA approval was based on findings from a multicenter, randomized controlled trial that was conducted in Italy and involved 700 participants between the ages of 40-80 years who were undergoing colonoscopy. A primary analysis of 263 patients found that colonoscopies that incorporated GI Genius technology identified precancerous and cancerous polyps in 55.1% of patients (polyps were later confirmed in the laboratory), compared to 42% of patients who underwent standard colonoscopy. The GI Genius did result in more biopsies being performed overall, though no additional adverse events were reported to be associated with the additional biopsies. There was also a slight increase in the number of suspected precancerous polyps that were biopsied and turned out not to be precancerous at all.

Overall, studies do show that even for well-trained clinicians, missed polyps remains a concern. With the FDA approval of the AI device, clinicians can now be equipped with a tool that can help to minimize the risk of missed colorectal polyps.

**Take away message:**

The FDA recently approved an artificial intelligence tool called the “GI Genius” that can be used during a colonoscopy to improve clinicians’ ability to detect precancerous and cancer polyps.

[READ THE FULL ARTICLE](#)

[WATCH THE VIDEO](#)

**Periodontal disease can be a potential risk indicator for colorectal cancer**

April 2021

Periodontal disease (PD) is a set of inflammatory conditions that affect the gums and bone that surround and support the teeth. PD is believed to increase systemic inflammation, trigger immune dysfunction, alter the body’s microbiome, and increase the chances of developing certain cancers, including colorectal cancer (CRC)<sup>5</sup>.

<sup>5</sup> Periodontal disease, tooth loss and colorectal cancer risk: Results from the Nurses’ Health Study

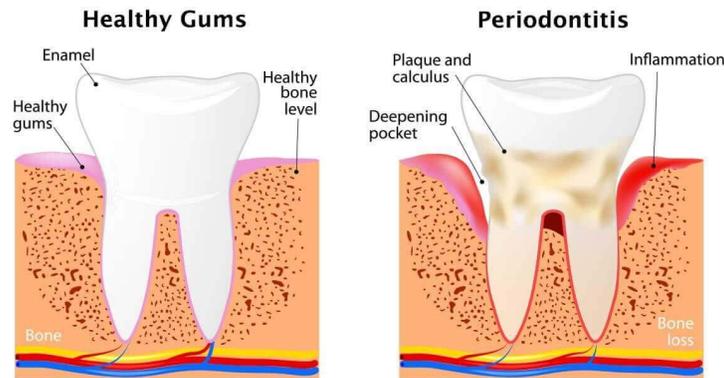
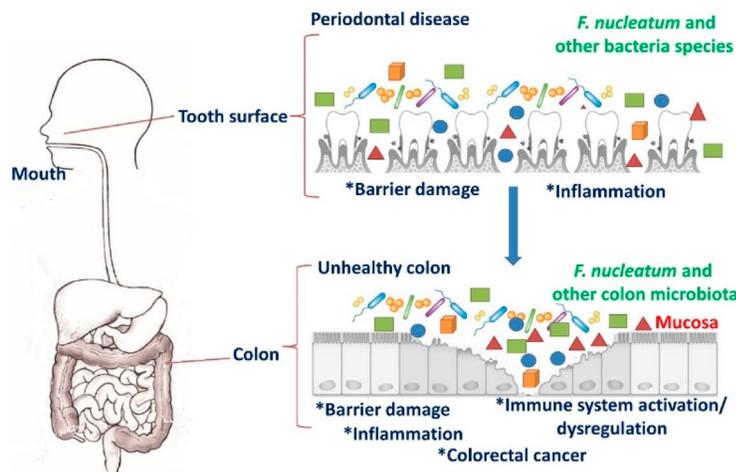


Image source: [nhdentalsurgery.com](http://nhdentalsurgery.com)

A 2016 study analysed data from the Nurses' Health Study and aimed to evaluate the relationship between PD and CRC incidence. The Nurses' Health Study is among the largest research studies ever conducted to investigate the risk factors for major chronic diseases. The investigators found that the risk of developing CRC increased by as much as 48% in women with periodontal disease, and cancer risk increased with the severity of tooth loss<sup>5</sup>.

A 2021 Chinese study published in the *Journal of Clinical Periodontology* aimed to evaluate the association between PD and CRC by examining all existing studies that assess PD and CRC risk. From their analysis, PD was associated with a 44% increase in risk for developing CRC<sup>6</sup>. These findings establish an association, but further studies will be needed to assess any causal relationship between PD and CRC.

### Periodontal disease, *Fusobacterium*, and CRC development



Migration of *F. nucleatum* and other bacterial species from the mouth to the colon

Image source: <https://www.mdpi.com/2072-6694/11/10/1592/htm>

<sup>6</sup> <https://onlinelibrary.wiley.com/doi/epdf/10.1111/jcpe.13402>

*Fusobacterium nucleatum* normally lives in the human oral cavity and is commonly associated with periodontal disease<sup>7</sup>. It is one species of bacteria that has been widely studied – its presence has been confirmed in and around CRC tumours (primary and metastatic), as well as other diseases such as cardiovascular disease, arthritis, and Alzheimer’s disease. Numerous investigations have confirmed high levels of other bacteria such as *Bacteroides*, *Prevotella*, *Leptotrichia*, *Clostridium difficile*, *Streptococcus gallolyticus*, *Bacteroides fragilis*, *Enterococcus faecalis*, *Campylobacter* spp., *Escherichia coli*, and *Streptococcus bovis* in CRC compared to normal healthy tissue, and *F. nucleatum* has been found to be synergistically associated with other bacteria to promote the incidence and development of CRC<sup>7</sup>. Specifically, it is implicated in CRC tumours’ ability to proliferate and evade immune attack<sup>8</sup>. Patients with CRC have higher levels of *F. nucleatum* compared to the general population, and the higher the levels, the worse the prognosis<sup>9</sup>.

The scientific data support the possibility of an association between periodontal disease and the development of CRC through the action of *F. nucleatum*, though the exact role of this specific bacterium in CRC progression remains an ongoing debate. Findings from future studies that investigate the relationship between periodontal disease and CRC could be important for both periodontal and gastrointestinal practice, integrating periodontal and CRC screening as part of a more comprehensive cancer screening regimen.

#### **Take away message:**

Various studies have shown that disease of the gums and the bones that surround and support our teeth (periodontal disease) has been associated with an increased risk of developing colorectal cancer (CRC). Whether periodontal disease *causes* CRC is not known, though some studies have pointed to the presence and action of a bacterium, *Fusobacterium nucleatum*, as one of the possible links between periodontal disease and the increased risk of developing CRC.

[READ THE FULL ARTICLE](#)

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<sup>7</sup> Targeting programmed *Fusobacterium nucleatum* Fap2 for colorectal cancer therapy  
<https://www.mdpi.com/2072-6694/11/10/1592/htm>

<sup>8</sup> Wu, J.; Li, Q.; Fu, X. *Fusobacterium nucleatum* Contributes to the Carcinogenesis of Colorectal Cancer by Inducing Inflammation and Suppressing Host Immunity. *Transl. Oncol.* 2019, 12, 846–851.

<sup>9</sup> Could periodontal disease through periopathogen *Fusobacterium nucleatum* be an aggravating factor for gastric cancer?  
<https://pubmed.ncbi.nlm.nih.gov/33260439/>

## Safety and efficacy of 7 days on/7 days off vs 14 days on/7 days off schedules of capecitabine in patients with metastatic colorectal cancer

April 2021

Capecitabine (Xeloda) is a chemotherapy drug that is taken as a pill by mouth for the treatment of metastatic colorectal cancer (mCRC). It is part of the class of cancer drugs called **fluoropyrimidines**, which include 5-fluorouracil (5-FU), a standard intravenous chemotherapy drug. This class of drugs works by interfering with cancer cells' ability to divide, causing them to die.



Capecitabine was developed in response to the need for therapeutic options that offer improved efficacy, tolerability, and convenience for patients. It was designed to mimic the continuous infusion of 5-FU and has a unique mechanism of activation that results in the release of the active ingredient specifically within the tumour tissue, therefore minimizing exposure of healthy tissues to systemic 5-FU<sup>10</sup>. Furthermore, capecitabine simplifies how chemotherapy is given to patients, providing more convenient therapy that can be administered on an outpatient basis, avoiding the complications and discomforts of intravenous chemotherapy.

Even though capecitabine is generally more tolerable than intravenous 5-FU, the regimen can still cause intolerable toxicities that may cause patients to reduce or delay their treatment. The standard treatment for patients with mCRC includes a regimen of 14 days receiving the drug followed by 7 days off (14/7) in a 21-day cycle. A recent study aimed to determine the tolerability of a different dosing regimen – 7 days of capecitabine therapy followed by 7 days off (7/7) – among patients with mCRC. Among the 175 patients, patients who received the standard dosing regimen were significantly more likely to ask for a dose reduction or a treatment delay compared to patients who received the novel dosing regimen. The occurrence of any adverse effects was significantly higher in the 14/7 group. No significant difference was found with respect to overall response rate to treatment, or survival outcomes.

Findings from this study showed that the 7/7 dosing schedule for capecitabine had a significant impact on increasing tolerability of the treatment and reducing adverse events, thereby enabling

<sup>10</sup> First-line oral capecitabine therapy in mCRC: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin

[https://www.annalsofncology.org/article/S0923-7534\(19\)61878-8/fulltext](https://www.annalsofncology.org/article/S0923-7534(19)61878-8/fulltext)

patients to adhere to it for longer. While no difference was found between the efficacy of the standard dosing schedule and the novel schedule, studies of longer duration will be needed to confirm these findings.

**Take away message:**

Capecitabine is a chemotherapy drug commonly used to treatment metastatic colorectal cancer (mCRC). Despite being better tolerated overall compared to standard intravenous 5-FU chemotherapy, it can still cause intolerable adverse effects and the need for treatment reduction or delays in some patients. Findings from a study showed that by changing how capecitabine is given to patients in a 21-day cycle, it was able to be better tolerated without affecting its effectiveness against the cancer.

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**Molecular characteristics of early onset colorectal cancer appear to vary by race**

April 2021

Disparities or differences in the incidence of early onset CRC among diverse population groups have become more pronounced. Findings from a recent study presented at the virtual American Association for Cancer Research Annual Meeting found that Black patients with early onset microsatellite stable (MSS) colorectal cancer (CRC) had significantly higher tumour mutational burden (TMB) compared to white patients. This study aimed to explore the biology that drives CRC incidence across these groups so that more targeted therapeutic approaches may be developed in the future.

In the study, the investigators examined the unique mutational patterns by race in over 5,000 patients with CRC included in a publicly accessible international cancer registry of real-world data from 12 worldwide institutions. Young black patients were found to carry a higher TMB, meaning that they have a greater number of total mutations or changes in the DNA of their cancer cells compared to other patients. TMB is being used as a biomarker to help plan the best treatment for a given patient, and tumours that show high numbers of mutations are more likely to respond to certain types of immunotherapy. Research has shown that MSS tumours that show high TMB show benefit from immunotherapy such as pembrolizumab<sup>11</sup>. A better understanding of TMB can help to plan a patient's best treatment options by targeting distinct molecular features, facilitating a precision medicine approach and hopefully closing the gaps in disparities between subgroups of young patients diagnosed with CRC. The investigators highlight that despite identifying potential biological factors that influence the incidence of early-onset CRC, "distinct early-onset CRC patterns across diverse population subgroups reflect a complex interplay of biology, genetics, behaviours and social determinants of health".

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<sup>11</sup> Microsatellite-stable tumours with high mutational burden benefit from immunotherapy  
<https://pubmed.ncbi.nlm.nih.gov/31405947/>

**Take away message:**

The rising incidence of early onset CRC has drawn attention to the fact that cancer disparities between diverse population populations have become more pronounced. Black early onset CRC patients were found to have different mutations and mutational burden compared to white and Asian early onset CRC patients. This study helps to shed light on molecular differences that exist between early onset CRC patient groups by race, with the hope that future precision medicine approaches can help to close the gaps in health disparities among young CRC patients.

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